REMARKS

The Office Action dated May 20, 2003 presents the examination of claims 1-9. Claims 10-25 are withdrawn from consideration. Claim 9 is canceled. Claims 26-28 are added. Support for claim 26 is found in claim 1; support for claim 27 is found on page 8, lines 7-8 of the specification; support for claim 28 is found on page 8, lines 12-16. No new matter is inserted into the application.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner rejects claims 1-8 under 35 U.S.C. § 112, second paragraph for allegedly being indefinite. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Specifically, the Examiner rejects claims 1, 3, and 5 for being confusing. In response to the Examiner's remarks, Applicants amend claims 1-7 so that the claims particularly point out and distinctly claim the inventive subject matter of the present application.

In addition, the Examiner states that claim 9 cannot be examined because it does not recite the elected SEQ ID NO:3. Claim 9 is canceled, thus rendering the issue moot.

Rejection under 35 U.S.C. § 103(a)

The Examiner rejects claims 1-8 under 35 U.S.C. § 103(a) for allegedly being unpatentable over Kawai et al. (*Human Immunology*, 41:121-126 (1994)), in view of GenBank Accession Number X97645 (December 2, 1996), and in further view of Tokunaga et al. (*Human Immunology*, 47:103 (1996)), and Zammatteo et al. (Analytical Biochemistry, 236:85-94(1996)). Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Kawai et al. teaches microtiter plate hybridization. GenBank Accession Number X97645 contains SEQ ID NO:3 at positions 79-97. Tokunaga et al. teaches using microtiter plate hybridization for typing HLA alleles. Zammatteo et al. teaches hybridization in microtiter plates. None of the cited references teach a method wherein a typing table is generated based upon signal patterns. To make up for this deficiency in the prior art, the Examiner states, "[I]t was well known in the art that hybridization patterns can define unique characteristics of a gene or allele of interest." Applicants respectfully disagree.

The Examiner has failed to establish a *prima facie* case of obviousness. In order to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981 (CCPA 1974). In the instant case, none of the prior art references disclose a typing table for HLA class I alleles. Thus, this

claim limitation has not been taught or suggested by the prior art. The Examiner improperly relies on "common knowledge" or "common sense" to make up for the deficiency in the prior art. In this regard, Applicants direct the Examiner's attention to MPEP § 2144.03, which states that reliance on common knowledge in the art or "well known" prior art should only be used in limited circumstances. U.S. Pat. & Trademark Off., Manual Pat. Examining Proc. § 2144.03 (8th ed. Rev. 1, 2003). Such circumstances only occur when the facts beyond the record are "capable of such instant and unquestionable demonstration as to defy dispute." In re Ahlert, 424 F.2d 108, 1091 (CCPA 1970).

In the instant case, it is improper for the Examiner to rely on "common knowledge" without providing a reference that actually shows a typing table generated for typing HLA alleles. The Examiner merely relies on U.S. Patent 5,645,990 which uses a mathematical formula to determine paternity. U.S. '990 does not result in the generation of a typing table. See also In re Lee, 277 F.3d 1338, 1344-45 (Fed. Cir. 2002), wherein the Federal Circuit stated, "The board cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies." Since the Examiner has failed to establish a *prima facie* case of obviousness, the rejection is improper and should be withdrawn.

In any event, Applicants respectfully submit that the present invention is not obvious over a hypothetical combination of the cited references. The method of the present invention is the first for typing HLA class I with oligonucleotide probes. As shown on pages 2-3 of the specification, several HLA class I DNA typing methods have been reported, such as PCR-RFLP. However, these methods require complicated manipulation, strict reaction conditions, and skill. Methods for typing HLA class II are described in Kawai et al., *Human Immunology*, 41:121-126, 1994. However, as shown on pages 2-3 of the specification, the development of a PCR-based method for HLA class I DNA typing has been remarkably delayed, compared to PCR-based methods for HLA class II typing. The reasons for this delay are as follows:

(1) While almost all of the class II gene mutations (i.e., gene substitutions), including those which reflect the specificity of antigens, concentrate in the region of exon 2, the class I gene mutations are interspersed among the regions of exons 2 and 8, or exon 4; and

(2) The HLA class I genes, including non-classical genes (i.e., HLA-E, -F, and -G) and pseudogenes (HLA-H, -J, -K, and -L), are highly homologous to one another.

As such, it has been difficult in the field to develop a PCR-based method for HLA class I typing.

Furthermore, in this field of technology, the selection of primers and probes is generally difficult. Kawai et al. fails to

teach such selection of primers and probes for HLA class I typing. Thus, the skilled artisan could not achieve the present invention, even if the same method for HLA class II DNA typing is known. Tokunaga et al., *Human Immunology*, 47:103 (1996), fails to disclose whether or not PCR-SSOP is used for HLA class I typing. However, as shown in *Human Immunology*, 47:121-126 (1994), the same authors actually used PCR-SSOP for typing class II, but not for typing class I. Zammatteo et al. discloses the covalent grafting of DNA probes onto microwells. However, the DNA probes utilized by Zammatteo et al. are phosphorylated, rather than amino-modified, as used in the present invention. Thus, the cited references fail to disclose and/or teach the method of the present invention. In other words, no reference teaches and/or discloses a PCR-based method for HLA class I typing. Therefore, the instant claims are not obvious over the cited references.

With respect to claims 5-7, Applicants respectfully point out that hybridization is performed in the presence of formamide (claim 5). Claim 6 recites that hybridization is performed in a solution containing formamide at a temperature of 37°C. Claim 7 recites that the temperature for washing after hybridization is at room temperature. Conversely, in the prior art hybridization is usually performed at a comparatively high temperature, such as about 65°C, to improve binding specificity. The hybridization temperature utilized in U.S. '990 was 55-56°C, 60°C in Kawai et al., and 50°C in Zammatteo et al. The washing temperature was

65°C in Kawai et al. and 50°C in Zammatteo et al. Formamide was not utilized in the hybridization solution of Kawai et al., nor in that of Zammatteo et al. By the use of a solution containing formamide in the present invention, hybridization can be performed at lower temperatures, i.e. 37°C, and washing can be done at room temperature without heating (as shown on page 8 of the specification). None of the cited references disclose or suggest a method wherein hybridization and washing may be performed at low temperatures by the use of solutions containing formamide. As such, each of claims 5-7 are non-obvious over the cited prior art.

In claim 8, the probes used for typing human HLA class I are recited. GenBank Accession Number X97645 cited by the Examiner is *B. taurus* MHC (a bovine gene). Although the sequence of GenBank Accession Number X97645 and that of the probe represented by SEQ ID NO:3 overlap, the genetic information of *B. taurus* MHC does not teach or suggest that a probe overlapping with this sequence can be used for HLA class I typing.

For all of the above reasons, Applicants respectfully submit that the pending claims are patentable over Kawai et al. (*Human Immunology*, 41:121-126 (1994)), in view of GenBank Accession Number X97645 (December 2, 1996), and in further view of Tokunaga et al. (*Human Immunology*, 47:103 (1996)), and Zammatteo et al. (Analytical Biochemistry, 236:85-94(1996)). Withdrawal of the instant rejection is therefore respectfully requested.

Conclusion

Applicants respectfully submit that the above amendments and/or remarks fully address and overcome the rejections of record, such that the present application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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